A randomized trial of amitriptyline and mexiletine for painful neuropathy in HIV infection

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Article abstract—*Background:* Painful sensory neuropathy is a common complication of HIV infection. Based on prior uncontrolled observations, we hypothesized that amitriptyline or mexiletine would improve the pain symptoms. *Method:* A randomized, double-blind, 10-week trial of 145 patients assigned equally to amitriptyline, mexiletine, or matching placebo. The primary outcome measure was the change in pain intensity between baseline and the final visit. *Results:* The improvement in amitriptyline group (0.31 ± 0.31 units [mean ± SD]) and mexiletine group (0.23 ± 0.41) was not significantly different from placebo (0.20 ± 0.30). Both interventions were generally well tolerated. *Conclusions:* Neither amitriptyline nor mexiletine provide significant pain relief in patients with HIV-associated painful sensory neuropathy.

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Painful distal sensory neuropathy is a common complication of HIV infection.[1-6] Between 20 and 35% of patients with HIV infection are reported to eventually develop distal sensory neuropathy. The annual incidence of neuropathy in patients with HIV infection and CD4 counts below 200/mm^3 is approximately 5%.[7] The symptoms and signs of painful neuropathy are generally consistent: pain primarily on the soles and dorsum of the feet, decreased primary sensory modalities in the feet, decreased ankle reflexes, and minimal intrinsic foot weakness. Frequently there are associated electrophysiologic abnormalities, especially diminished sural nerve sensory action potentials.

The cause of painful neuropathy in HIV infection is unknown. A direct viral etiology has been proposed, and a recent study demonstrates direct viral invasion of peripheral nerve.[8] Antiviral therapy, including dideoxynucleoside analogs, can also cause or worsen painful neuropathy. Treatment of painful neuropathy in HIV infection has had limited success. Although painful neuropathy associated with vasculitis may respond to prednisone, this is not known to be of any benefit in primary HIV neuropathy.[9] A double-blind, placebo-controlled trial of peptide T found no benefit in the treatment of painful neuropathy.[10] In the absence of positive studies in patients with HIV-related neuropathies, clinicians commonly treat these patients' pain based on reports of efficacy in other neuropathic pain conditions. Amitriptyline has been demonstrated to reduce pain associated with diabetic[11] and other neuropathies[12] not including HIV-associated syndromes. Possible mechanisms of analgesia include potentiating the inhibitory effects of norepinephrine and possibly serotonin on central processing of pain[13] or blocking sodium channels mediating ectopic discharges from injured axons or cell bodies of peripheral nerve fibers.[14-15] Mexiletine, a sodium-channel blocking drug closely related to lidocaine, has been reported to reduce pain in diabetic neuropathy[16-17] and in other neuropathic pain conditions.[18]

We conducted a randomized, double-blind, parallel group clinical trial to assess the short-term safety and effectiveness of amitriptyline and mexiletine in reducing pain intensity in patients with HIV-related painful distal neuropathy.

*See the Appendix on page 1687 for a list of members of the AIDS Clinical Trial Group 242 Protocol Team.

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Methods. *Organization.* This study was organized and conducted by the Neurologic AIDS Research Consortium (NARC) and the AIDS Clinical Trial Group (ACTG) at 24 participating units. Informed consent was obtained from all subjects in accordance with the review boards at each participating center. An independent performance and safety monitoring board periodically reviewed the safety of the study.

Recruitment and enrollment. A total of 145 subjects were enrolled in the trial between July 1994 and December 1996. Participating sites enrolled between 1 and 12 patients each. Patients considered eligible were those who had HIV infection and clinical symptoms and signs sufficient for a diagnosis of painful neuropathy defined as 1) primary symptoms of symmetrical pain, burning or tingling discomfort in the feet for at least 2 weeks, and rated on the pain intensity scale as at least mild all the time or moderate for a total of at least 2 hours per day; and, additionally, either 2) diminished or absent ankle reflexes or 3) distal diminution of vibratory sense or diminished pain and temperature sensation in the legs as assessed by study clinicians, many not being neurologists. Additional inclusion criteria included being on a stable dosage (if taken by the subject) of dideoxynucleoside analogs for at least 8 weeks before randomization and of cimetidine for at least 2 weeks before randomization and having serum liver function enzyme levels less than five times the upper limit of normal. Patients were excluded if their painful neuropathy was clearly attributable to another neuropathic drug (e.g., cisplatin, nitrofurantoin), if they were taking cardiac antiarrhythmic agents or tricyclic or tetracyclic antidepressants, or if they had a greater than 50% change in the dosage per week of medications for pain control in the week before entry. Patients with diabetes mellitus, documented history of cardiac disease, or EKG demonstrating a malignant arrhythmia and those with a history of seizure disorder were excluded.

Subjects were randomly assigned, by a computer-generated list, at the baseline evaluation to one of three treatment groups: 1) amitriptyline, 2) mexiletine, or 3) placebo. There was a 4-week titration period, then a 4-week stable treatment period followed by a tapering of study medications over 1 week. The subjects, investigators, and coordinating staff were unaware of the individual treatment assignments.

Therapy and follow-up. The subjects took gelatin capsules containing 25 mg of amitriptyline, an inactive placebo, or an active placebo containing 0.125 mg of benztropine chosen to mimic the dry mouth caused by amitriptyline. Mexiletine (Boerhinger-Ingelheim, Ridgefield, CT) was provided in 150-mg gelatin capsules or matching inactive placebo. Experimental treatments were started on the day of randomization. Subjects were assigned to receive active amitriptyline and placebo mexiletine, placebo amitriptyline and active mexiletine, or the active control (benztropine) for amitriptyline and placebo mexiletine. Subjects then titrated up their study medications over a 4-week period beginning with one capsule of mexiletine or matching placebo in the evening and one capsule of amitriptyline or matching placebo in the evening, escalating up to a maximum of two capsules of mexiletine or matching placebo twice daily and four capsules of amitriptyline in the evening. The maximum possible dosage of 100 mg of amitriptyline may be near the optimal dosage for analgesia.[19-20] The dosage was not increased if complete pain relief was achieved or if intolerable side effects were reported. After this 4-week titration period, subjects remained on their achieved dosage for a subsequent 4 weeks and then tapered off their medication in the reverse order of the upward titration. Each down titration step of one capsule was accomplished in one day.

Table 1 *Gracely pain intensity scale*

Letter	Verbal descriptor	Numeric level
A	Nothing	0
B	Faint	0.4
C	Very weak	0.36
D	Weak	0.45
E	Very mild	0.59
F	Mild	0.74
G	Moderate	1.09
H	Barely strong	1.10
I	Slightly intense	1.33
J	Strong	1.36
K	Intense	1.54
L	Very intense	1.64
M	Extremely intense	1.77

Subjects were reevaluated at 2, 4, 8, and 10 weeks after randomization. At each visit, vital signs, laboratory safety tests, and EKGs were performed, and the analgesic intake and experimental drug diaries and pain diaries (see below) were reviewed with the subject. Drug levels were obtained at weeks 4 and 8, and a neurologic examination and Karnofsky scale were performed at baseline and at week 8.

Sites were monitored to ensure the quality of the data collected in the research records and the accuracy of the data in the database and to determine whether all regulatory requirements were met.

Outcome measures. Subjects rated current pain intensity twice daily by choosing from a list of 13 words that describe the intensity of pain. The words had been assigned numeric values on the basis of ratio-scaling procedures that demonstrated good internal consistency, reliability, and objectivity.[21] The values corresponding to the verbal descriptors are listed in table 1 and represent logarithm base-10 transformed values of the originally proposed numeric values.[21] The scale has distinguished active from control interventions in studies of experimental and clinical pain.[22] A mean score was calculated from the 14 ratings for the baseline week and each week of treatment. The primary measure of efficacy in the study was the change in mean pain intensity from the baseline week to week 8. For patients not completing the full 8-week evaluation but completing at least 4 weeks, the last 7 days of available data were used. The primary measures of safety were the frequency and severity of clinical adverse experiences and laboratory test abnormalities and the frequency of dosage modification caused by adverse experiences.

Secondary measures of efficacy included changes between baseline and the final evaluation in mood, quality of life, and the requirement for additional analgesic agents.

Mood was measured by the Profile of Mood States, and quality of life was measured by the General Health Self-Assessment form. A global impression of pain relief was also recorded by subjects.

Subjects were allowed to take common opioid and nonopioid analgesics (excluding tricyclic antidepressants) according to the usual practice of their physicians. Patients recorded all of their prescription and over-the-counter analgesic medications. The authors classified these medications according to the World Health Organization's three-step analgesic ladder, in which *no medications* is step 0, *acetaminophen or nonsteroidal anti-inflammatory drugs* is step 1, *low-dose codeine, oxycodone, hydrocodone in combination with acetaminophen, or nonsteroidal anti-inflammatory drugs (NSAIDs)* is step 2, and *stronger preparations of opioids such as morphine, fentanyl, hydromorphone, or methadone* is step 3. To define whether subjects' analgesic medications had increased, decreased, or remained stable between baseline and the last week of treatment for which analgesic data was available, the following algorithm was used: 1) If the highest WHO step included in a subject's medications changed, a change in that direction was recorded; 2) a change limited to a variation in dose of acetaminophen and various NSAIDs was considered "no change" as there is no consensus on relative potency among different NSAIDs; and 3) if there was a change in the dose of any opioid (step 2 or 3), the total daily opioid doses for the baseline and final weeks were calculated using standard opioid analgesic equivalence tables,[23] and any increase or decrease in the total opioid dose was considered significant.

Monitoring of compliance was performed at follow-up by evaluations by counting the number of unused tablets returned by the subject. Compliance was also measured by serum levels of study medications during the weeks of active treatment.

Statistical analysis. Statistical analysis was based on all subjects who were randomized, took at least 1 dose of assigned treatment, and completed at least the 4 weeks of dose titration phase (study week 4). The primary endpoint was the pain intensity difference from baseline to week 8 or last week on-study (if that was at least study week 4). The treatment effect on pain difference from baseline was tested by analysis of variance where treatment and change in analgesic medication use were the main effects. Analyses of categorical indices were based on Fisher's exact test, and nonparametric methods were used in tests involving numerical indices.

The original sample size estimate was 240 subjects, giving 80% power to detect a 0.16 difference among treatment groups on the Gracely scale, assuming a common standard deviation of 0.35 units (on the logarithmic scale). After a second interim review of the data (a first review was inconclusive and the study was not interrupted), the monitoring board recommended that the study close after 145 subjects were enrolled because further enrollment was unlikely to detect a significant difference between the active arms and placebo. This decision was based on baseline to week 8 changes in pain intensity and a cut-off boundary computed according to the method of O'Brien and Fleming.[24]

Results. *Comparability of treatment groups.* The treatment groups were similar at baseline with regard to demographic and clinical measures (table 2). There were no differences in the amount or type of analgesic medications used among the treatment groups.

Safety and tolerability of experimental medications. There were no significant differences between the placebo-treated group and any treatment group regarding changes in ECGs or laboratory test abnormalities. There were no differences in the numbers of or reasons for premature discontinuations among the treatment groups (figure 1). There were differences among the treatment groups regarding time to study discontinuation (data not shown). Amitriptyline was associated with sedation requiring dosage modification (n = 10), and mexiletine was associated with nausea and vomiting requiring dosage modification (n = 10); neither phenomenon was observed in the placebo group. Other reasons for dosage modification included confusion (amitriptyline = 1, placebo = 2), dizziness (mexiletine = 1), urinary retention (mexiletine = 3, placebo = 1), and other less common events (amitriptyline = 4, mexiletine = 8, placebo = 3). In the amitriptyline and mexiletine groups approximately 70% of subjects achieved the maximum dosage. Overall, both amitriptyline and mexiletine were well tolerated.

Efficacy measures. Of the 145 subjects enrolled, 126 completed at least the initial 4-week titration phase of the study and hence were included in the efficacy analysis. There were no significant changes in the measures of pain intensity among the treatment groups. The amitriptyline group (n = 39) improved by 0.31 ± 0.31 (mean ± SD) units; the mexiletine group (n = 44) improved by 0.23 ± 0.41 units; and the placebo group (n = 43) improved by 0.20 ± 0.30 units ($p = 0.38$). The mean reduction in pain intensity with amitriptyline, relative to placebo, was thus 0.11 units; the difference between "mild" and "moderate" pain is 0.35 units. Although the changes did not achieve statistical significance, there was a trend toward improvement in the amitriptyline-treated group. When examined on a week-by-week basis (figure 2), there appeared to be a larger and more consistent reduction in pain scores in the amitriptyline group compared with either the mexiletine group or the placebo group, although these differences did not reach statistical significance at any time point in the study.

Secondary measures. There was no significant change in the global assessment of pain relief (table 3). Similarly, there was no change in the mood or quality of life assessments (data not shown). There was no difference among the groups regarding changes in analgesic medications (table 4). Subjects with less improvement in pain scores were more likely to increase analgesic intake (data not shown). The mean serum amitriptyline levels (12 to 24 hours post-dose) were 148.8 ± 191.7 μg/mL (mean ± SD) at week 4 (n = 26) and 141.0 ± 190.4 μg/mL at week 8 (n = 17). The mean mexiletine levels were 0.50 ± 0.38 μg/mL at week 4 (n = 24) and 0.30 ± 0.28 μg/mL at week 8 (n = 19). There was no association between the serum levels of study drugs and the amount of pain relief (data not shown).

Compliance and blinding. Compliance with experimental medications varied by visit between 80 and 100% of total tablets dispensed. There were no differences in compliance among the groups. Analysis of drug levels indicated that there was no surreptitious use of either amitriptyline or mexiletine in those assigned to other

Table 2 *Baseline characteristics*

	Amitriptyline, n = 47	Mexiletine, n = 48	Placebo, n = 50	*p* Value‡
Age, y, median	39	40	43	0.37
Male sex, n (%)	45 (96)	47 (98)	47 (94)	0.70
ace/ethnicity, n (%)				
White	33 (70)	35 (73)	32 (62)	0.33
Black	12 (26)	7 (14)	12 (24)	
Hispanic	2 (4)	6 (12)	4 (8)	
Other	0	0	2 (4)	
Karnofsky score, median	90	80	80	0.06
CD4 count, cells/mm^3, median	54	73	54	0.86
Prior toxic antiretroviral* use, n (%)				
Current	16 (34)	17 (35)	16 (32)	0.99
Discontinued 8–26 wk	11 (23)	11 (23)	13 (26)	
Never used/discontinued > 26 wk	20 (43)	20 (42)	21 (42)	
Pain medication use: WHO step classification,† n (%)				
0	18 (38)	16 (33)	19 (38)	0.29
1	15 (32)	17 (36)	15 (33)	
2	11 (23)	14 (29)	12 (24)	
3	3 (6)	1 (2)	4 (8)	
Baseline pain levels, mean Gracely Scale (SE)	1.02 (0.05)	1.06 (0.04)	1.13 (0.04)	0.12

* Patients were stratified by prior use of ddI, ddC, d4T.
† See text for description of World Health Organization analgesic classification.
‡ *p* Values calculated by Fisher's exact test for categorical variables, Kruskal-Wallis test for continuous variables except for baseline pain intensity (F test).

treatment groups. There were no instances of emergency unblinding of study medications.

Discussion. The data from this clinical trial demonstrate that amitriptyline at dosages of up to 100 mg per day and mexiletine at dosages up to 600 mg per day are generally well tolerated in subjects with HIV infection and painful distal sensory neuropathy. Neither intervention provided a statistically significant improvement in pain intensity scores compared with the placebo intervention, although there is a trend for improvement in the amitriptyline group.

In two studies of amitriptyline in diabetic neuropathy that used the same pain intensity scale,[11,22] amitriptyline was superior to placebo by 0.25 and 0.18 units compared with the 0.11 units reduction in pain observed in the current study. Our finding that amitriptyline is relatively ineffective in HIV-associated neuropathies is supported by a preliminary report from another multicenter study in HIV-infected patients.[25] It is possible that the distinct neuropathologic features of the HIV-associated distal painful neuropathy[26] generate ectopic discharges that resist the analgesic actions of amitriptyline or mexiletine.

There are several limitations in this study. The study sample size was smaller than originally planned. Study enrollment was discontinued on the recommendation of the safety committee that suggested that even with full enrollment the trial would not be able to demonstrate a statistically significant benefit of either intervention. The variability of the outcome measure and the magnitude of the placebo response was somewhat larger than that anticipated in the initial sample size calculation, and this observation has important implications for sample size calculations for future HIV neuropathy studies. Painful HIV neuropathy, as we defined it for the purposes of this study, is a relatively heterogeneous disorder. More precise definition of neuropathy syndromes (e.g., HIV-related, nucleoside-related) may alter the response to interventions.

Although one might speculate that higher doses of amitriptyline or mexiletine may have produced greater pain relief, there has been only one prospective dose-response study of amitriptyline, and none of mexiletine in neuropathic pain. McQuay et al.[19] showed that in a mixed group of patients with neuropathic and other chronic pain conditions, amitriptyline 75 mg/day was superior to 25 mg/day, but no higher doses were studied. Sindrup et al.[20] studied the dose-response relationship of doses up to 350 mg/day of a similar tricyclic, imipramine, in 15 patients with diabetic neuropathy, and reported that pain relief approaches a maximum at about 125 mg/day. The mean serum concentrations achieved in

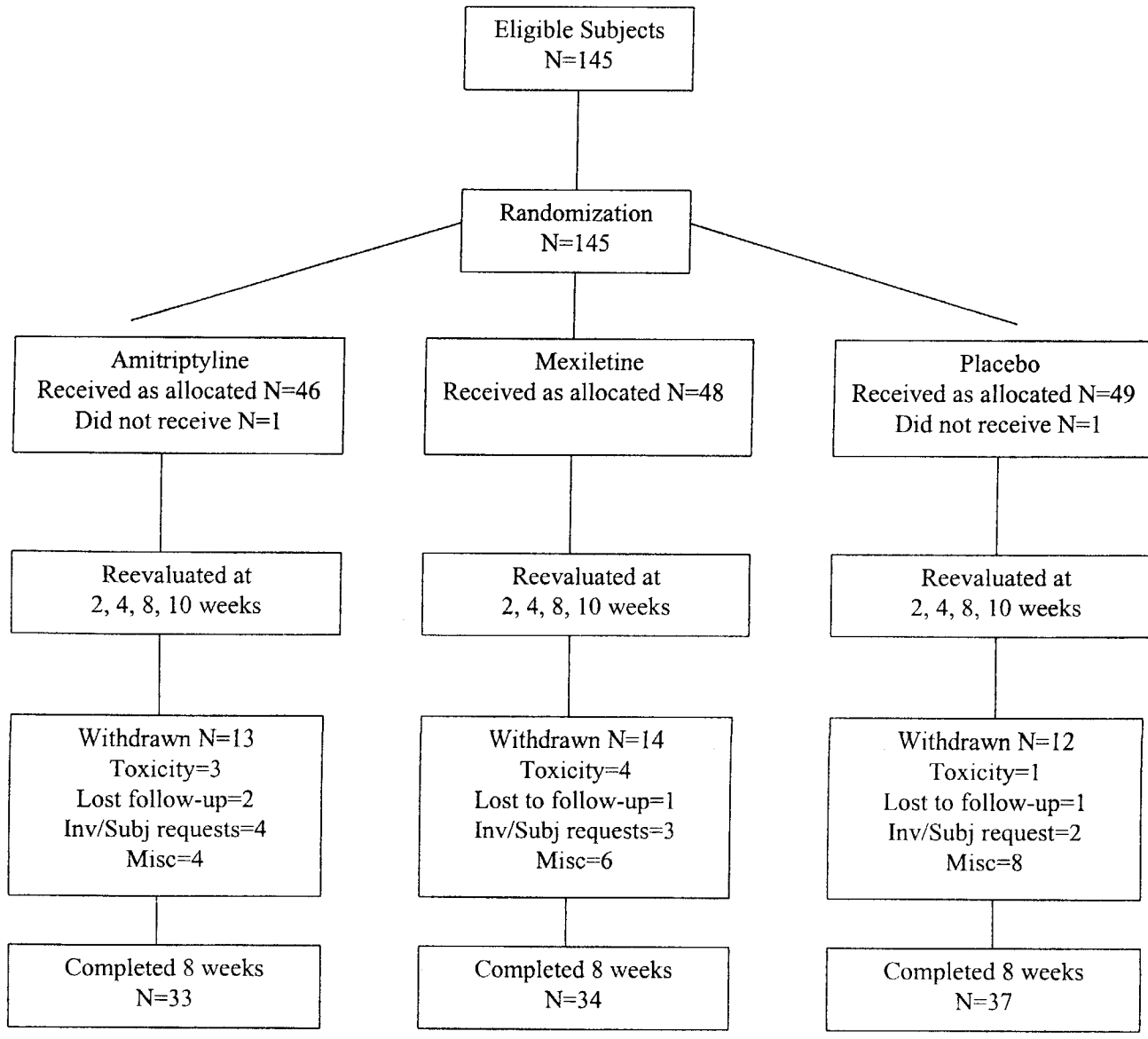

Figure 1. Flowchart of participation in the trial.

this study have been associated with pain relief in diabetic neuropathy.[22] Although clinicians continue to provide anecdotal reports of pain improvement with amitriptyline, it did not have statistically demonstrable benefit in this controlled study. For current clinical practice, physicians will need to balance the findings of possible benefit in some patients with the potential toxicity of these interventions. We do not know if our findings are generalizable to other tricyclic antidepressants.

Some investigators have advocated higher doses of mexiletine than used in this study and target the serum concentrations, 0.5 to 2.0 μg/mL, often used for treatment of cardiac arrhythmias.[27] The mean serum concentrations achieved in this study were at the lower end of this range. However, the 20% incidence of mexiletine dose modification because of nausea and vomiting in our study underscores the difficulty in using higher dosages. This may be owing to mexiletine's nonselective effects on brain, heart, and other sodium channels, prompting efforts to develop blockers that are selective for peripheral nerve sodium channels.[28]

The incidence of HIV-associated sensory neuropathy will likely continue to increase as patients are surviving longer with potent antiviral therapy, often

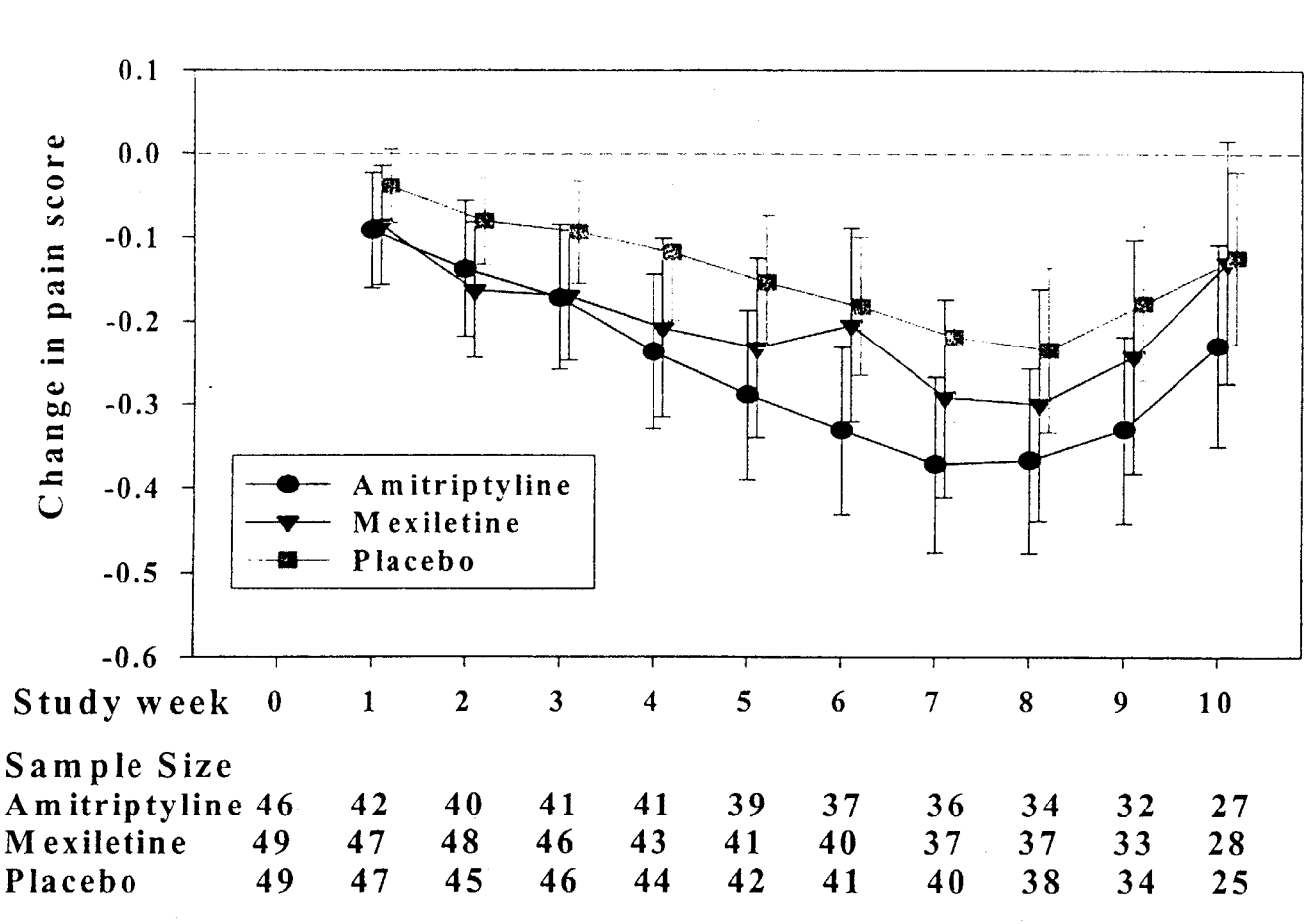

Figure 2. Pain change from baseline. A random effects (growth-curve) model was fitted to all weekly available data (pain difference from baseline to each week considered). Treatment and change of analgesic use (increased use versus constant or decreased use, as compared with baseline) and baseline pain intensity were the fixed effects, whereas a random parabola (second-degree polynomial) was fitted to each subject's weekly pain intensity data to account for the nonconstant trend in pain change that was seen in all treatment arms (improvement during the first 8 weeks followed by deterioration during the last 2 weeks). The p *value for treatment is 0.2415.*

Table 3 *Global assessment of pain relief from baseline to week 8*

	Treatment, n (%)			
	Total, n = 144	Amitriptyline,* n = 46	Mexiletine,* n = 48	Placebo,* n = 50
Complete relief	8 (7)	3 (9)	4 (11)	1 (2)
A lot of relief	32 (29)	13 (38)	11 (30)	8 (20)
Moderate relief	29 (26)	7 (21)	7 (19)	15 (37)
Slight relief	17 (15)	6 (18)	5 (14)	6 (15)
No relief	20 (18)	4 (12)	8 (22)	8 (20)
Pain is worse	6 (5)	1 (3)	2 (5)	3 (7)

* *p* Value 0.164 comparing amitriptyline, mexiletine, and placebo; Kruskal-Wallis test.

Table 4 *Change in pain medications, baseline to follow-up (week 4 or higher)*

Change in pain medications	Treatment, n (%)			
	Total	Amitriptyline*	Mexiletine*	Placebo*
Decrease	24 (19)	7 (17)	7 (17)	10 (23)
No change	65 (51)	22 (54)	23 (52)	20 (47)
Increase	39 (30)	12 (29)	14 (32)	13 (30)

**p* Value 0.920 comparing amitriptyline, mexiletine, and placebo.

containing peripheral neurotoxic agents. Because neither this study nor the peptide T trial[10] identifies an effective intervention for painful neuropathy, this remains a major untreated cause of disability in patients with advanced HIV infection. Further investigations are necessary to establish both symptomatic and restorative therapy. The ACTG has recently completed a trial of human recombinant nerve growth factor for patients with painful HIV-related neuropathy, and the analysis is anticipated in June 1998. However, simple, inexpensive, and easily administered symptomatic therapy is still needed for the treatment of this common condition. Other medications shown to relieve neuropathic pain in conditions unrelated to HIV infection, such as opioids,[29-30] NMDA receptor antagonists,[31-32] and gabapentin,[33] are worthy of study in patients with HIV-related neuropathy pain.

This study demonstrates that a placebo-controlled study design is feasible in patients with HIV-related sensory neuropathy. In addition, the collection of the pain intensity measures on daily diaries was easily accomplished and appears to be a useful outcome measure for clinical trials.

Appendix

The ACTG 242 Protocol Team consisted of the following individuals and institutions: Core Team—Karl Kieburtz, MD, chair; David Simpson, MD, vice chair; Constantin Yiannoutsos, PhD, statistician; Mitchell Max, MD, David Clifford, MD, investigators; Peter Jatlow, MD, pharmacologist. National Institute for Allergies and Infectious Diseases, Division on AIDS (DAIDS)—Pat Kasdan, Sharon Shriver, protocol specialists, Ana Martinez, RPh, pharmacist. Data Management—Linda Millar and Dodi Colquhoun; Larry Zaborski (statistician). Pharmaceutical representative (Boerhinger-Ingelheim)—Virgil Dias, PharmD. National Institute for Neurological Disorders and Stroke (NINDS) Performance and Safety Monitoring Board—Burk Jubelt (Chair), John Noseworthy, Bruce Barton, Leroy Sharer, Al Kerza. Participating AIDS Clinical Trial Units (ACTUs)—D. Simpson, K. Sperber, E. Chusid, P. Gerits, Mt. Sinai, New York; R.J. Ellis, D. Richman, University of California San Diego; J. Lund, A.C. Collier, D. Cummings, C. Marra, University of Washington; R.R. McKendall, R.B. Pollard, M. Borucki, P. Galatas, University of Texas at Galveston; E.J. Singer, E.N. Miller, M. Guerrero, G. Beall, UCLA Medical Center; G.J. Dal Pan, J.C. McArthur, K. Carter, B. Becker, J.G. Bartlett, Johns Hopkins; M. Gould, M. Glicksman, M. Roy, Washington University; T. Tucker, Case Western Reserve; B.A. Cohen, C. Cooper, J. Phair, N. French, J. Pulvirenti, Northwestern University; University of Pennsylvania; University of California San Francisco; H.H. Balfour, Jr., University of Minnesota; L.J. Wheat, Indiana University; S. Raffanti, D. Greenspan, Meharry University; C.D. Hall, W. Robertson, C. Kapoor, University of North Carolina; M.S. Hirsch, Harvard University; University of Colorado; M.A. Fischl, University of Miami; R. Reichman, R. Hewitt, G. Schifitto, University of Rochester; Charity Hospital; R. Soeiro, Montefiore (Einstein); C. Shikuma, University of Hawaii; M.S. Saag, University of Alabama Birmingham; Howard University.

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